American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:197–201 (1996)

Familial Alcoholism in Manic-Depressive (Bipolar) Disease

George Winokur, William Coryell, Jean Endicott, Martin Keller, Hagop Akiskal, and David Solomon
National Institute of Mental Health Collaborative Program on the Psychobiology of Depression – Clinical Studies, Washington, D.C.

A previous analysis found a relatively high rate of alcoholism in a cohort of bipolar I subjects, and a trend for increased rates of alcoholism in relatives of subjects with both bipolar I disorder and alcoholism, compared to relatives of subjects with bipolar I disorder and no alcoholism. The sample of subjects with bipolar I disorder has been enlarged through continued follow-up, permitting new analyses to address the association and heritability of bipolar I disorder with alcoholism. Probands with bipolar I disorder were followed for 10 years as part of the NIMH Collaborative Depression Study. The rate of alcoholism in relatives of probands with both bipolar I disorder and alcoholism was compared to the rate of alcoholism in relatives of probands with bipolar disorder and no alcoholism. The prevalence of alcoholism in relatives of subjects with bipolar I disorder was compared to the rate of alcoholism in relatives of control subjects. Relatives of probands with bipolar I disorder showed a higher rate of alcoholism than relatives of controls. Relatives of probands with bipolar I disorder and alcoholism showed a higher rate of alcoholism than relatives of probands with bipolar I disorder without alcoholism. These data suggest that familial alcoholism may contribute to a vulnerability to bipolar I disorder, and that there is a shared heritability for the two disorders. © 1996 Wiley-Liss, Inc.

KEY WORDS: familial alcoholism, bipolar, mania, hyperactivity

INTRODUCTION

In a recent follow-up and clinical study of alcoholism in bipolar patients, we found that the observed rate of alcoholism in bipolars was far higher than would be expected from a comparison group [Winokur et al., 1995]. We found no significant differences between alcoholic and nonalcoholic bipolar patients in family history of independent alcoholism or affective disorders. "Independent alcoholism" is defined as the presence of alcoholism in the absence of bipolar I disorder. This suggested that alcoholism might be best viewed as a phenomenon secondary to the bipolarity itself. There were decreases in familial alcoholism as one went from patients with bipolar/alcoholism to bipolar disorder only to comparison subjects, but these were not significant ($P = 0.07$, which was erroneously presented as $P = 0.7$ in the published paper). The alcoholism of bipolar illness was far more likely to remit in a 5-year period than was alcoholism seen as a primary illness. This suggested that the alcoholism of bipolar illness was qualitatively different than primary alcoholism.

In light of this trend, it seemed useful to reexplore the possibility that bipolars who are alcoholic might show more familial independent alcoholism than bipolars who are not alcoholic. We had access to a 33% increase in the number of bipolar alcoholics, which made a reassessment possible. Also, we were able to address the following questions: if there is significantly more independent alcoholism in families of bipolar patients vs. families of comparison subjects, could a case be made that alcoholism and bipolar disorder might share a common genetic etiology?

The data for the above study came from the Collaborative Depression Study (CDS). At intake, 231 bipolar

Received for publication July 31, 1995; revision received October 20, 1995.

This study was conducted with the participation of the following investigators: M.B. Keller, M.D. (Chairperson, Providence); W. Coryell, M.D. (Co-Chairperson, Iowa City); H.S. Akiskal, M.D., J.D. Maser, Ph.D. (Washington, DC); P.W. Lavori, Ph.D., T.I. Mueller, M.D., M.T. Shea, Ph.D. (Providence); J. Fawcett, M.D., W.A. Scheftner, M.D. (Chicago); G. Winokur, M.D., J. Haley (Iowa City); J. Endicott, Ph.D., A. Leon, Ph.D., J. Loth, M.S.W. (New York); J. Rice, Ph.D., T. Reich, M.D. (St. Louis). Other contributors include: N.C. Andreasen, M.D., Ph.D., P.J. Clayton, M.D., J. Croughan, M.D., G.L. Klerman, M.D. (deceased), R.M.A. Hirschfeld, M.D., M.M. Katz, Ph.D., E. Robins, M.D. (deceased), R.W. Shapiro, M.D. (deceased), R.L. Spitzer, M.D., and M.A. Young, Ph.D.

This manuscript has been reviewed by the Publication Committee of the Collaborative Depression Study and has its endorsement.

Address reprint requests to George Winokur, M.D., Department of Psychiatry, UIHC, 2887 JPP, Iowa City, IA 52242.

or schizoaffective mania patients were identified and of these, 70 had bipolar disorder together with alcoholism [Winokur et al., 1995]. We were able to increase the number of bipolar probands by using 10-year follow-up data, and we had a 6-year follow-up on relatives. By using the follow-up material, we were able to add further alcoholics (from 70 to 93) to those patients who had bipolar illness, and also to add further bipolars who had never been manic at time of intake but became manic in follow-up. Likewise, the 6-year follow-up of relatives added new bipolars and alcoholics to the family data; in the prior study, the family interviews only included those that had been accomplished at the time of the beginning of the study. In this paper, we explore the question of whether bipolar/alcoholic patients have more independent alcoholism in their families than bipolar/nonalcoholic patients, in order to determine if the increased data might clarify prior trends. If a family history of independent alcoholism were increased, we can test the meaning of the finding by comparing familial alcoholism in bipolar patients vs. controls, and by comparing familial bipolarity in bipolar/alcoholic patients vs. bipolar/nonalcoholic patients.

A finding of hyperactivity in the bipolar/alcoholic patients' childhood would favor an increased genetic propensity for alcoholism in bipolar illness. An adoption study favors the association of childhood hyperactivity and adult alcoholism. Goodwin et al. [1975] found that alcoholics as children were more often hyperactive, truant, antisocial, shy, aggressive, disobedient, and friendless. Morrison and Stewart [1971] found a high prevalence of antisocial personality, hysteria and alcoholism, and hyperactivity itself in biological parents of hyperactive adoptees. In the hyperactive probands, 5% of mothers and 20% of fathers were alcoholic, respectively, but in control children, none of the mothers and 10% of the fathers were alcoholic. Cantwell [1972] found a large increase in alcoholism in parents of hyperactive children. We will present data on attention-deficit/hyperactivity disorder in the probands, as this is relevant to family background.

SUBJECTS AND METHODS

The probands were part of the National Institute of Mental Health Collaborative Depression Study (CDS) and were evaluated at Harvard University, Columbia University, Rush Medical College, Washington University, and the University of Iowa. Approximately three quarters were hospitalized patients and one quarter were newly evaluated patients from outpatient clinics. To enter the study, they had to meet criteria for mania, major depression (primary or secondary), or schizoaffective disorder. Diagnoses were made according to the Research Diagnostic Criteria (RDC) [Spitzer et al., 1978] using all sources of information. These patients were interviewed with the Schedule for Affective Disorder and Schizophrenia (SADS) [Endicott and Spitzer, 1978]. The probands were prospectively followed at 6-month intervals for 5 years and thereafter annually for a maximum of 10 years of follow-up. Follow-ups were conducted using the Longitudinal Interval Follow-up Evaluation (LIFE), which records psychopathology and treatment and psychosocial functioning [Keller et al., 1987].

A subset of probands voluntarily participated in a family study, and relatives of consenting probands were interviewed with the SADS-Lifetime Version (SADS-L). Diagnoses were made using the RDC, as with the probands. Besides the data from personally interviewed relatives, at intake the probands and relatives were systematically evaluated about their family history of psychiatric illness, using the Family History Research Diagnostic Criteria (FH-RDC). A consensus diagnosis was made on family members using all available information. These family histories were updated at a 5-year follow-up interview of the proband in order to capture new familial disorders that had occurred, as well as disorders that may have been missed at intake [Andreasen et al., 1986, 1987; Endicott et al., 1975].

A comparison group (N = 469) was matched to a subset of first-degree relatives directly interviewed as part of the family study. Each relative provided the names of 6 acquaintances of similar age, sex, and economic status, and these were contacted in random order until a willing subject was identified. The mean number of potential controls who needed to be contacted was approximately 2. There were no exclusion criteria. These comparison subjects were evaluated with the SADS-L. This acquaintanceship method yielded a comparison group that tended to be somewhat younger and contained more women than the total study group of interviewed relatives; there was no evidence of assortative acquaintanceship by presence of mental disorder in this group.

The probands in this study (N = 277) met criteria for a lifetime diagnosis of bipolar disorder or schizoaffective mania at admission to the study or in the follow-up. Schizoaffective manic patients were included with bipolar I patients because the family history of psychiatric illness, the course, and response to treatment show considerable similarity [Coryell, 1994]. The probands were divided into those who, in addition to bipolarity, fulfilled the diagnosis of alcoholism vs. those who did not (N = 93 [34%] vs. N = 184 [66%]). These numbers take into account those probands who became manic in the 10-year follow-up, some of whom also had had or developed alcoholism. Some relatives also developed bipolar illness and had had or developed alcoholism in the 6-year follow-up. No bipolar II probands were included in this study because they are not consistently related to bipolar I disorder [Coryell et al., 1984].

Alcoholism encompasses both alcohol abuse and dependence. An evaluation of the symptoms of alcoholism in bipolar/alcoholic probands showed considerable severity, with both multiple social consequences and withdrawal symptoms [Winokur et al., 1995]. Because of the fact that there is the possibility that bipolarity itself may cause alcoholic behavior, a hierarchical method was used in the family study. Alcoholism to be counted in this study had to occur independently, i.e., without an accompanying bipolar illness in a person.

In comparing rates of alcoholism in personally-interviewed relatives and comparison subjects, we used Kaplan-Meier estimates (life tables to time of onset of psychiatric illness) [Kalbfleisch and Prentice, 1980]. This method included all relatives and comparison sub-

jects through the time some of them became depressed, manic, or alcoholic, or left the study through being lost to follow-up, thus minimizing the effects of censored data. Relatives or comparison subjects who had been ill or dropped out were no longer counted, thus leaving only those who remained at risk for illness and were still being followed up. Wilcoxon χ^2 statistics were used as nonparametric tests for differences to time to illness.

In the current study the diagnosis of hyperactivity was made by interviewing the proband. The reliability of this retrospective method of assessing hyperactivity has been reported by Loney and Kramer [1992].

In accordance with the rules of the National Institute of Mental Health and the participating centers, all subjects provided informed consent.

RESULTS

On the variables of age and sex we were then able to match 93 patients who had bipolar illness plus alcoholism to 93 patients who had bipolar illness only. For the assessment of the relatives, we used data obtained in a 6-year follow-up. Table I presents a comparison of bipolar/alcoholic probands with bipolar nonalcoholic probands who were matched for age and sex at intake. Matched groups were used because 65% of the bipolar/alcoholic group were males as opposed to 38% of the bipolar/nonalcoholic group ($P < 0.001$), and the bipolar/nonalcoholic group was 2½ years older than the bipolar/alcoholic group ($P = 0.12$). The only significant finding in the table is that bipolar/alcoholic probands have a significantly earlier age of onset for affective illness. Figure 1 presents a life table comparison for all first-degree relatives and for siblings only, between the relatives of bipolar alcoholics and relatives of bipolar nonalcoholics. As may be noted with the addition of new data, there is a clear finding of increased independent alcoholism in the relatives of bipolar alcoholic patients as opposed to the relatives of nonalcoholic bipolar patients. By the 6-year follow-up (circa 1984), the probands were between age 41.4–43.5 years; relatively few children in the family study passed through the age of risk. Of the first-degree family members the siblings were most likely to be evaluated.

TABLE I. Clinical Characteristics: Bipolar/Alcoholic vs. Bipolar/Nonalcoholic Probands Matched for Age and Sex

	Bipolar/ alcoholic	Bipolar/ nonalcoholic	*P*
Male/female	60/33	60/33	
Age at intake, mean (SD)	35.0 (11.3)	35.1 (12.3)	NS
Age of onset, first affective episode, mean (SD)	22.7 (7.87)	26.5 (12.0)	.01
Age of onset, first mania,[a] mean (SD)	28.6 (10.4)	31.3 (12.4)	.11
Follow-up, months, mean (SD)	95.3 (39.0)	90.3 (42.8)	NS
N affective episodes during follow-up, mean (SD)	2.36 (2.31)	2.27 (2.6)	NS
N manic[a] episodes during follow-up, mean (SD)	1.89 (2.68)	1.78 (2.65)	NS

[a] Includes schizoaffective manic episodes.

Because a case can be made that there is a problem of statistical independence in comparing the proportion of ill family members between the two groups, we have evaluated the two groups on the basis of the parents, but have used the material obtained by the systematic family history using the Family History Research Diagnostic Criteria. These data are presented in Table II, and the findings there support the life table findings. The parents of probands with bipolar I disorder and alcoholism are far more likely to have independent alcoholism. There is a trend for an increased rate of mania in parents of bipolar/nonalcoholic probands as compared to parents of bipolar/alcoholic probands.

Childhood Background as Related to Alcoholism in the Bipolar Patient

The probands were systematically evaluated for the presence of a childhood hyperactive syndrome which was defined as a self-report of at least two of the following five traits: restlessness, hyperactivity, impulsiveness, short attention span, and short fuse for anger. It was possible to match 89 bipolar I alcoholic probands for age and sex with bipolar nonalcoholic probands and 25 bipolar alcoholic relatives for age with 25 bipolar nonalcoholic relatives. The comparisons are presented in Table III, separated for male and female subjects. Comparing only the matched pairs, the bipolar/alcoholic group showed hyperactivity in 31.5% vs. 19.8% in the bipolar/nonalcoholic group ($P = 0.07$). As may be noted, the findings support an increased amount of a childhood hyperactive syndrome in bipolar patients who have alcoholism as well.

The Question of Assortative Mating in Parents of Bipolar Probands

A reasonable explanation for the increase in alcoholism in bipolar patients would be assortative mating. This could be tested by an evaluation of manic and nonmanic mothers of probands and of the frequency with which the fathers of probands were alcoholic, and by an evaluation of manic and nonmanic fathers and of the frequency with which the mothers are alcoholic. Of 8 manic mothers, 3 (27%) of the fathers are alcoholic; of 278 nonmanic mothers, 27% of the fathers are alcoholic. Of 16 manic fathers, none of the mothers are alcoholic (0%), and of 262 nonmanic fathers, 7 (3%) of the mothers are alcoholic. One can conclude that evidence in favor of assortative mating leading to alcoholism in bipolar probands is lacking.

Familial Alcoholism (Independent Alcoholism) in Controls vs. Relatives of Bipolar Patients

There were 277 probands and 467 controls on whom we obtained a family history. In a comparison of families, it was clear that independent alcoholism is more frequent in relatives of bipolar probands (both with and without alcoholism) than in relatives of controls. These data are presented in Table IV. Though the families of bipolars without alcoholism were higher for indepen-

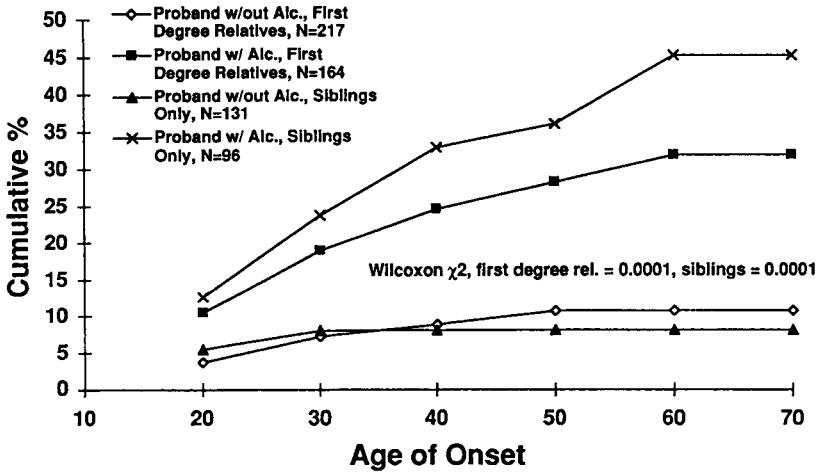

Fig. 1. Development of independent alcoholism in relatives of bipolar probands with and without alcoholism.

dent alcoholism than the comparison families, the difference is not significant.

DISCUSSION

Using a substantially-expanded data set (a 33% increase in the number of bipolar alcoholics and a 20% increase in the number of bipolars) from our last effort to evaluate the family background in bipolar patients who also suffered from alcoholism, we have compared them to the family background of bipolar patients who have never shown alcoholism. The findings are as follows: bipolar disorder/alcoholism shows an increased family background for independent alcoholism by use of the life table method; bipolar patients with alcoholism show an earlier age of onset; looking at the family history and family study material in matched groups that have bipolar disorder/alcoholism and bipolar disorder without alcoholism, there is an increase in parental history of independent alcoholism in the former and a trend toward an increase in mania in the latter. Bipolar disorder/alcoholism is related to attention-deficit/hyperactivity disorder in the probands' history. Assortative mating between a parent with alcoholism and a parent with mania does not account for the higher frequency of alcoholism in bipolar probands. Independent alcoholism is more frequently seen in the families of bipolars than in families of controls.

The increase in independent familial alcoholism in bipolar illness could be related to two possibilities. First, it is conceivable that assortative mating occurs and that alcoholic parents may be somehow more likely to mate with a spouse that has a susceptibility to bipolar illness. Our data suggest that this is unlikely. Another possibility is that alcoholism in itself constitutes part of the familial or genetic heritage which leads to bipolar illness. To test the latter hypothesis, we evaluated the parents of two groups of bipolar probands matched for age and sex, those with bipolar alcoholism themselves and those with bipolar nonalcoholism. It was clear that the probands with bipolar alcoholism had a highly significant increase in parental alcoholism (Table II). There was a trend suggesting that patients who lacked the alcoholism associated with bipolarity had a higher parental prevalence of bipolar illness itself. This suggests that if bipolar illness is transmitted by additive genetic factors, one of these factors may manifest itself by alcoholism. The parent with bipolar illness, however, would have considerably more of such susceptibility factors and consequently there is less need for the alcoholic parent to add to the risk.

TABLE II. Psychiatric Illness in Parents of Matched Patients With Bipolar Disorder/Alcoholism vs. Bipolar Nonalcoholism*

	Bipolar/ alcoholic (N = 93)	Bipolar/ nonalcoholic (N = 93)	χ^2	P
N parents	186	185		
N (%) bipolar, SAM	6 (3.2)	14 (7.3)	3.34	0.07
N (%) depression, SAD	31 (16.8)	43 (23.1)	2.35	0.13
N (%) independent alcoholics[a]	42 (22.7)	21 (11.3)	8.57	0.003

* SAM, schizoaffective manic; SAD, schizoaffective depressive. d.f. = 1 in all cases.
[a] Alcoholism in the absence of lifetime bipolar illness.

TABLE III. Childhood Hyperactive Syndrome in Bipolar/Alcoholic vs. Bipolar/Nonalcoholic Patients Matched for Age

	Bipolar/ alcoholic	Bipolar/ nonalcoholic	P
N[a] childhood hyperactive syndrome, N (%)	114 36 (32)	116 20 (17)	.01
N females childhood hyperactive syndrome, N (%)	39 12 (31)	50 6 (12)	.03
N males childhood hyperactive syndrome, N (%)	75 24 (32)	66 14 (21)	.15

[a] Contains 89 bipolar/alcoholic probands matched for age and sex with 91 bipolar/nonalcoholic probands and 25 bipolar/alcoholic relatives matched for age with 25 bipolar/nonalcoholic relatives. Data on hyperactivity were missing for 2 bipolar/alcoholic probands.

TABLE IV. Positive Family History of Independent Alcoholism

	Number of families	N	(%)
Comparison families	467	135	(29)[a]
Proband families	277	121	(44)
Families of bipolar/alcoholic probands	93	58	(62)
Families of bipolar probands without alcoholism	184	63	(34)

[a] Comparison families vs. proband families, $\chi^2 = 16.82$, d.f. = 1, $P < 0.001$. Comparison families vs. families of bipolar probands without alcoholism, $\chi^2 = 1.77$, $P = 0.18$.

If bipolar illness were in part dependent on a genetic factor which also led to alcoholism, a comparison of relatives of a control group to the relatives of bipolar I subjects should show that the latter has an increased family history of alcoholism. This too was found (Table IV). Because a bipolar patient could receive a higher genetic complement from a bipolar parent, if such a bipolar parent were lacking, chance would dictate an increase in parental alcoholism to complete the complement.

The bipolar disorder/alcoholism group is more likely to have an earlier onset, which suggests the possibility that drinking in itself may precipitate the illness in some cases.

Attention-deficit/hyperactivity disorder by history might not be easily distinguishable from cyclothymic mood swings. Akiskal et al. [1977] found that alcohol abuse was present in about half of the cyclothymic probands that he studied. Those authors favored the hypothesis of alcohol use as a form of self-treatment. Alcohol problems do precede the onset of bipolar disease in about 50% of bipolar/alcoholics, and findings by Akiskal et al. [1977] that cyclothymic probands abused alcohol frequently could be one of the possible explanations of the association between attention-deficit/hyperactivity disorder and alcoholism, related to the idea that cyclothymia and hyperactivity might be difficult to separate by history.

There are some other studies that are relevant to the relationship between bipolar illness and alcoholism. Nurnberger et al. [1994] presented data from the Collaborative Study on the Genetics of Alcoholism (COGA). In alcohol-dependent subjects there is a statistically significant increase in mania when compared to subjects who were nonalcohol-dependent. This would support the hypothesis that alcoholism and mania may have a common etiology to some extent. In the same study, however, the relatives of probands with alcoholism did not have a significant increase in mania over the relatives of probands without alcoholism.

In another study of the relationship between bipolar disorder and alcoholism, Maier et al. [1995] found "no convincing evidence" that there were any shared familial components between bipolar disorder and alcoholism. However, this study was considerably different from ours, in that most of the patients who showed manic episodes, 39 out of 44, were considered bipolar II patients. Also in Maier et al. [1995], in the relatives of bipolar patients plus alcoholism vs. a control group, there was an increase of alcoholism without bipolar illness. This would be similar to our concept of independent alcoholism.

The mechanism by which alcoholism may exert its influence on bipolar illness is unknown. Previous data [Winokur et al., 1995] suggested the possibility that excessive drinking may provide an insult to the individual which in turn produces the mania. Another possibility is that bipolar disorder and alcoholism share a common genetic propensity, in which case we would expect a higher familial incidence of alcoholism in bipolar patients than in controls. The data presented in this paper support the possibility that a genetic propensity for alcoholism may produce familial alcoholism only, but in combination with other unrelated genetic factors it may add to the risk for bipolar illness.

REFERENCES

Akiskal H, Djenderedjian A, Rosenthal R, Khani K (1977): Cyclothymic disorder: Validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 134:1227–1233.

Andreasen N, Rice J, Endicott J, Reich T, Coryell W (1986): Family history approach to diagnosis: How useful is it? Arch Gen Psychiatry 43:421–429.

Andreasen N, Rice J, Endicott J, Coryell W, Grove W, Reich T (1987): Familial rates of affective disorder: A report from the National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 44:461–469; correction (1988), 45:776.

Cantwell D (1972): Psychiatric illness in families of hyperactive children. Arch Gen Psychiatry 27:414–417.

Coryell W (1994): Schizoaffective and schizophreniform disorders. In Winokur G, Clayton P (eds): "The Medical Basis of Psychiatry," 2nd ed. Philadelphia: W.B. Saunders, pp 115–129.

Coryell W, Endicott J, Reich T, Andreasen N, Keller M (1984): A family study of bipolar II disorder. Br J Psychiatry 145:49–54.

Endicott J, Andreasen N, Spitzer R (1975): "Family History Research Diagnostic Criteria." New York: New York State Psychiatric Institute, Biometrics Research, pp 1–20.

Endicott J, Spitzer R (1978): A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 35:837–844.

Goodwin D, Schulsinger F, Hermansen L, Guze S, Winokur G (1975): Alcoholism and the hyperactive child syndrome. J Nerv Ment Dis 160:349–353.

Kalbfleisch J, Prentice R (1980): "The Statistical Analysis of Failure Time Data." New York: John Wiley and Sons, Inc., pp 1–321.

Keller M, Lavori P, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen N (1987): The Longitudinal Interval Follow-up Evaluation: A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 44:540–548.

Loney J, Kramer J (1992): A checklist to assess the childhood hyperactivity and aggression of adult men. Society for Research in Child and Adolescent Psychopathology poster submission, Sarasota, Florida.

Maier W, Lichtermann D, Minges J, Bierbrauer J, Heun R (1995): The relationship between bipolar disorder and alcoholism: A controlled family study. Psychol Med 25:787–796.

Morrison J, Stewart M (1971): A family study of the hyperactive child syndrome. Biol Psychiatry 3:189–195.

Nurnberger J, Reich T, Tipp J, Hesselbrock V, Crowe R, Schuckit M, DePaulo JR, Blehar M, Gershon E, Begleiter H (1994): Comorbidity between alcoholism and affective disorder in systematically ascertained samples. Poster presented at the American College of Neuropsychopharmacology, San Juan, Puerto Rico.

Spitzer R, Endicott J, Robins E (1978): Research Diagnostic Criteria: Rationale and reliability. Arch Gen Psychiatry 35:773–782.

Winokur G, Coryell W, Akiskal H, Maser J, Keller M, Endicott J, Mueller T (1995): Alcoholism in manic depressive (bipolar) illness: Familial illness, course of illness in the primary-secondary distinction. Am J Psychiatry 152:365–372.